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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

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(54) Use of β-Carbolines

(72) Huth, Andreas - Germany (Federal Republic of) ;
Krüger, Martin - Germany (Federal Republic of) ;
Rahtz, Dieter - Germany (Federal Republic of) ;
Seidelmann, Dieter - Germany (Federal Republic of) ;
Turski, Lechoslaw - Germany (Federal Republic of) ;
Löschmann, Peter-Andreas - Germany (Federal Republic of) ;
Stephens, David-Norman - Germany (Federal Republic of) ;
Schneider, Herbert - Germany (Federal Republic of) ;

(71) Schering Aktiengesellschaft - Germany (Federal Republic of) ;

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(57) 9 Claims

ABSTRACT OF THE DISCLOSURE

The invention concerns the use of compounds of formula (I), in which R^3, R^4, R^9 and R^A are as defined in the description, as non-competitive glutamate antagonists in the preparation of a drug for the treatment of neurological and psychiatric disorders. The invention also concerns drugs containing these compounds, as well as the new compounds of formula (Ia) and a method of preparing them.

New Use of ß-Carbolines

The invention relates to the new use of ß-carbolines of formula I and their acid addition salts for the production of a pharmaceutical agent for symptomatic and preventive treatment of diseases that are based on defective glutamatergic neurotransmission in the central nervous system, pharmaceutical agents that contain these compounds as well as the new compounds of formula Ia and the process for their production.

From Biochem. Soc. Trans. 1989, Vol. 17, pp. 81-83, Neuroscience 1990, Vol. 3, pp. 799-807, Pharmacol. Biochem. Behav. 1989, Vol. 32, pp. 27-35, Psychopharm. 1989, Vol. 97, pp. 262-268 and Pharmacol. Biochem. Behav. 1992, Vol. 42, p. 401-405 it is known that ß-carbolines have a good affinity to the benzodiazepine receptors and have an antagonistic, inverse agonistic and agonistic effect on the properties known from the benzodiazepines. The known compounds of formula I are described, for example, in EP-30254, EP-A-54507, EP-A-130141, EP-A-137390, EP-A-222693, EP-A-234173, EP-A-232675, EP-A-237467, WO 92/21679 and DOS-4130933.2 as active ingredients or as initial compounds for the production of the active ingredients or as intermediate compounds. It can be gathered from these publications that ß-carbolines are distinguished by anxiolytic, anticonvulsive, antidepressive, sedative and anti-aggressive effectiveness and also have amnestic or memory-promoting properties.

In the central nervous system of mammals, included humans, high concentrations of excitatory amino acids such as glutamate and aspartate are present. For the excitatory amino acids there

exist different receptors that are designated corresponding to their specific agonists as N-methyl-D-aspartate (NMDA)-, Kainst (KA)- and quisqualate (QUIS)-receptor. The quisqualate receptors are also called AMPA-receptors according to the specific agonists (RS)-amino-3-hydroxy-5-methyl-4-isoxazolpropionate. The synaptic function of excitatory amino acid L-glutamate is mainly imparted by quisqualate receptors. Since the quisqualate receptor contains a modulation point that can influence the function of the ion canal, the effect on the modulation point of the quisqualate receptor makes possible a bidirectional influence of the receptor function.

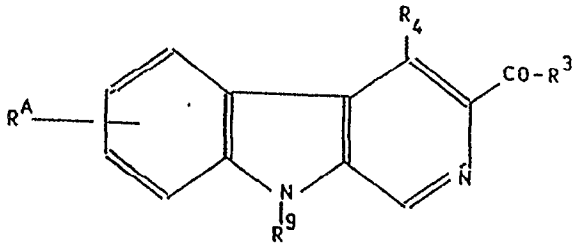
Clinical and animal-experimental findings indicate that increased or reduced glutamatergic neurotransmission occurs in the central nervous system in numerous neurological and psychiatric diseases.

The diseases that can be triggered by the dysfunction of the excitatory amino acids or changed glutamatergic neurotransmission include, for example, neurodegenerative disorders such as Parkinson's disease, Huntington's disease, Alzheimer's disease, senile dementia, multiinfarct dementia, amyotrophic lateral sclerosis, epilepsy, cell damage by hypoglycemia, hypoxia and ischemia; neuronal damages that result from uncontrolled movements; neuronal damages that are triggered by brain damage such as stroke, brain trauma and asphyxia as well as psychoses, schizophrenia, anxiety conditions, conditions of pain, migraines and emesis. Also functional disorders such as memory disorders (amnesia), learning process disorders, vigilance symptoms and

withdrawal symptoms after chronic intake of addictive agents such as benzodiazepines, hallucinogens, alcohol, cocaine and opiates are based on the dysfunction of glutamatergic neurotransmission.

Surprisingly it has now been found that the compounds of formula I act on the modulation points of the quisqualate receptor and correct the pathologically changed function of this receptor and thus can be used for symptomatic and preventive treatment of the diseases mentioned above.

According to the invention, suitable are compounds of formula I as well as their acid addition salts



I

in which

R^A means hydrogen, halogen, NH_2, NO_2, $-CHR^1-R^2$, phenyl, hetaryl, $-OR^5$ or -CO-R optionally substituted with halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy or amino and can be single to triple, the same or different,

R^3 means hydroxy, C_{1-6}-alkoxy or NR^6R^7,

R^4 means hydrogen, phenyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl or $-(CH_2)_n-O-R^8$ and

R^9 means hydrogen, C_{1-6}-alkyl or benzyl, and

R is hydroxy, C_{1-6}-alkoxy, benzyloxy or $NR^{10}R^{11}$, in which R^{10} and R^{11} are the same or different and mean hydrogen, C_{1-6}-alkyl,

C_{2-6}-alkenyl or together with the nitrogen atom a saturated 5 or 6 membered heterocycle that can also contain another sulfur, oxygen or nitrogen atom and can be substituted with phenyl or C_{1-4}-alkyl,

R^1 means hydrogen or C_{1-4}-alkyl,

R^2 means hydrogen, C_{1-2}-alkyl, -O-C_{1-6}-alkyl, -S-C_{1-6}-alkyl optionally substituted with $NR^{12}R^{13}$ or an optionally substituted phenyl, benzyl or phenoxy radical,

R^5 means hydrogen, C_{1-6}-alkyl, C_{3-7}-cycloalkyl or an optionally substituted phenyl, benzyl, hetaryl or benzo-condensed hetaryl radical,

R^6 means hydrogen, C_{1-6}-alkyl or C_{2-6}-alkenyl,

R^7 means hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, $NR^{14}R^{15}$, hydroxy, C_{1-6}-alkoxy, -CO-R^{16}, C_{3-7}-cycloalkyl, a phenyl or phenyl-C_{1-2}-alkyl radical optionally substituted with halogen or C_{1-6}-alkyl optionally substituted with C_{1-4}-alkoxy, $NR^{17}R^{18}$, hydroxy, halogen, phenyl, C_{1-4}-alkoxycarbonyl or hydroxycarbonyl and

R^6 and R^7 together with the nitrogen atom form a 3 to 6 membered saturated heterocycle, that can contain another O or N atom and can be substituted with one to two C_{1-4}-alkyl or C_{1-4}-alkoxycarbonyl, or

R^6 and R^7 together with the nitrogen atom form a 5 or 6 membered unsaturated heterocycle, that can contain another O or S atom or two more N atoms,

R^8 means hydrogen, C_{1-6}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl or phenyl,

R^{12} and R^{13} each mean hydrogen, phenyl, C_{1-4}-alkyl or together with the nitrogen atom form a 5 or 6 membered saturated

heterocycle that can contain another O, S or N atom and can be substituted with one to two C_{1-4}-alkyl or C_{1-4}-alkoxycarbonyl.

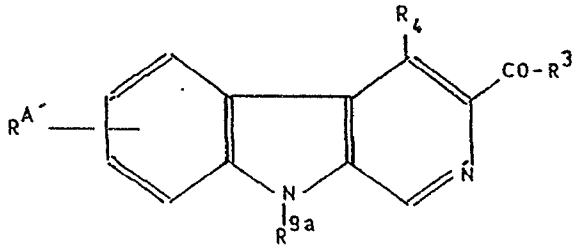
R^{14} and R^{15} have the meaning of R^{12} and R^{13},

R^{17} and R^{18} have the meaning of R^{12} and R^{13},

R^{16} means hydrogen, C_{1-4}-alkyl or NH_2 and

n means 1, 2 or 3.

Previously unknown compounds of formula I are the compounds of formula Ia



Ia

in which

R^{9a} means C_{1-6}-alkyl or benzyl,

$R^{A'}$ means phenyl, hetaryl, $-CHR^1-R^2$, $-OR^5$ or -CO-R optionally substituted with halogen, C_{1-4}-alkyl or C_{1-4}-alkoxy or amino and can be single to triple, the same or different and

R^1, R^2, R^3, R^4, R^5 and R have the above indicated meaning.

Substituent R^A can be in the A ring in position 5-8, preferably in 5, 6 and/or 7 position.

Alkyl contains in each case both straight-chain and branched-chain radicals such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec. butyl, tert. butyl, pentyl, isopentyl and hexyl.

Cycloalkyl can respectively stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

If R^5 or R^A means a hetaryl radical, then the latter is 5 or 6 membered and contains 1-3 heteroatoms such as nitrogen, oxygen and/or sulfur. For example, the following 5 and 6 ring heteroaromatic compounds can be mentioned: pyridine, pyrimidine, pyrazine, pyridazine, furan, thiophene, pyrrole, thiazole, imidazole, triazine.

If R^5 is a benzo-condensed hetaryl radical, then the latter contains 1-2 nitrogen atoms such as quinoline, isoquinoline, quinoxaline or benzimidazole.

The substituent of phenyl, benzyl and hetaryl radical R^5 can be single to triple in any position. Suitable substituents are halogens, nitro, cyano, C_{1-4}-alkyl, C_{1-4}-alkoxy, amino, C_{1-4}-alkoxycarbonyl, C_{1-4}-alkylthio and trifluoromethyl.

By halogen is to be understood respectively fluorine, chlorine, bromine or iodine.

As substituents of phenyl, benzyl and phenoxy radical R^2 the substituents of the aromatic compounds named for R^5 are suitable, especially halogen.

As phenyl-C_{1-2}-alkyl, for example, benzyl, phenethyl and α-methyl-benzyl can be mentioned.

As saturated nitrogen-containing heterocycle, respectively, for example, piperidine, morpholine, piperazine, pyrrolidine, imidazolidine, pyrazolidine and, if the heterocycle contains a sulfur atom, thiomorpholine and isothiazolidine are suitable. If

the heterocycle contains C_{1-4}-alkyl groups, then, for example, 2,6-dimethyl-morpholine and N-methyl-piperazine can be mentioned.

If R^6 and R^7 together with the nitrogen atom form a 5 or 6 unsaturated heterocycle, then, for example, imidazole, pyrrole, pyrazole are suitable.

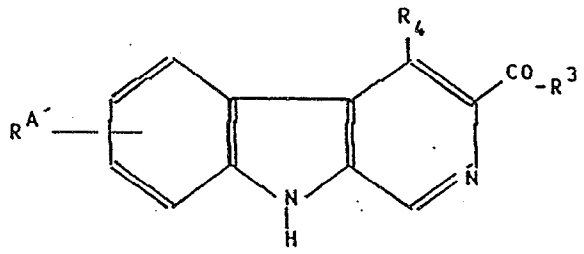
If chiral centers are present, the compounds of formula I can be present in the form of the stereoisomers and their mixtures.

The physiologically compatible acid addition salts are derived from the known inorganic and organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid, oxalic acid, glyoxylic acid as well as from alkane sulfonic acids such as, for example, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

If the substituent means $R^3{=}NR^6R^7$, then the following meanings for R^7 are to be considered as preferred: hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{3-7}-cycloalkyl, a phenyl or phenyl-C_{1-2}-alkyl radical optionally substituted with halogen, or C_{1-6}-alkyl optionally substituted with C_{1-4}-alkoxy, $NR^{17}R^{18}$, hydroxy, halogen, phenyl, C_{1-4}-alkoxycarbonyl or hydroxycarbonyl and R^6 and R^7 together with the nitrogen atom form a 3 to 6 membered saturated heterocycle, that can contain another O or N atom and can be substituted with one to two C_{1-4}-alkylcarbonyl or C_{1-4}-alkoxycarbonyl.

As substituent R^4, hydrogen, C_{1-6}-alkyl or $-CH_2-O-C_{1-6}$-alkyl are especially suitable.

The compounds of formula Ia can be produced in the same way as the previously known ß-carbolines, in which a compound of formula II



II

in which $R^{A'}$, R^4 and R^3 have the above-mentioned meaning, is optionally alkylated after protection of hydroxy groups with $R^{9a}X$, in which X means halogen, tosylate, mesylate or triflate, and optionally present protective groups are then cleaved off or esters are saponified.

For alkylation usual processes can be used as described, for example, in J. Org. Chem. 1986, 3172; J. Org. Chem. 1988, 4873 J. med. Chem. 1987, 1555 or Bull. Soc. Chem. Jpn. 1983, 280. The alkylation in the presence of bases such as alkali hydroxides, alkali hydride, alkali carbonate, alkali-tert.-butylate, that are used in excess, can be mentioned for example. The reactions can occur homogeneously or under solid-liquid or liquid-liquid phase transfer conditions. As solvents for the homogeneous reactions and the reactions occurring under solid-liquid phase transfer, solvents such as methylene chloride, dimethylsulfoxide, dimethylformamide or tetrahydrofuran are preferred, while in liquid-liquid phase transfer reactions, for example, methylene

chloride, benzene or toluene can be used. For phase transfer reactions a catalyst such as, for example, tetrabutylammonium hydrogen sulfate or aliquat 336 is advantageous.

As hydroxy protective groups all usually used protective groups are suitable that are not attacked under the reaction conditions. Examples of such protective groups for hydroxy protective groups present on the aromatic compound are benzyl, methoxymethyl, trialkylsilyl groups, for the carboxyl groups, alkyl ester, benzyl ester or tert.-butyl ester.

Depending on the type of protective groups the protective groups can optionally be removed while working-up the reaction mixture. For acid cleavages mineral acids and organic acids and their mixtures or tetrabutylammonium fluoride are suitable. Benzyl radicals are usually catalytically dehydrogenated e.g. with palladium/carbon. Alkyl esters can be hydrolyzed alkaline.

The isomer mixtures can be separated in the diastereomers and enantiomers according to the usual methods such as, for example, crystallization, chromatography or salt formation.

For formation of the physiologically compatible acid addition salts a compound of formula I is dissolved, for example, in a little alcohol and mixed with a concentrated solution of the desired acid.

If the production of the initial compounds is not described, they are known or can be produced analogously to known compounds or to the processes described here.

The initial compounds of formula II are obtained for example by hydrolysis of ß-carboline-3-carboxylic acid alkyl esters, then

amidation of the free carboxylic acid, optionally after conversion into a reactive acid derivative.

The production of ß-carboline-3-carboxylic acids takes place by usual acid or alkaline hydrolysis, for example, with aqueous alkali or alkaline earth solutions, optionally by addition of organic solvents such as alcohols at temperatures from room temperature to 150°C.

The amidation takes place on the free carboxylic acids or on their reactive derivatives such as, for example, acid chlorides, mixed anhydrides, imidazolides or azides by reaction with the corresponding amines at room temperature. If disubstituted amides are to be produced, they are advantageously reacted with the corresponding formamides at temperatures of 100-220°C.

The pharmacological effectiveness of the compounds of formula I was determined by the tests described below:

Male NMRI mice with a weight of 18-22 g were kept under controlled conditions (0600 - 1800 hours light/dark rhythm, with free access to food and water) and were randomly assigned to groups. The groups consisted of 5-16 animals. The observation of the spasms was performed between 0800 and 1300 hours.

Quisqualate was injected in the left ventricle of freely moving mice. The applicator consisted of a cannula with a device of stainless steel that limits the depth of the injection to 3.2 mm. The applicator was connected to an injection pump. The injection needle was inserted perpendicular to the surface of the skull according to the coordinates of Montemurro and Dukelow. The animals were observed up to the occurrence of clonic or tonic

spasms up to 180 seconds. The clonic movements that lasted longer than 5 seconds were counted as spasms. The beginning of the clonic spasms was used as the end point for the determination of the spasm threshold. The dosage that was necessary to increase or reduce the spasm threshold 50% ($THRD_{50}$) was determined in 4-6 experiments. The $THRD_{50}$ and the confidence limit were determined in a regression analysis.

By the example of 5-isopropoxy-4-methyl-9-methyl-ß-carboline-3-carboxylic acid ethyl ester (A) and by the example of 5-isopropoxy-4-methyl-ß-carboline-3-carboxylic acid ethyl ester (B) it can be gathered from the following table that the spasm threshold for quisqualate is increased (+) or decreased (-).

Table

compound	threshold determination ($THRD_{50}$(mg/kg)
A	+ 26.4 (20.0 - 33.9)
B	- 50.6 (25.0 - 102.1)

The results of these tests show that the compounds of formula I and their acid addition salts influence functional disorders of the glutamate receptor. Therefore they are suitable for the production of pharmaceutical agents for symptomatic and preventive treatment of diseases that are triggered by changing the function of the glutamate-receptor-complex.

In addition to the effects of the ß-carbolines known so far, the compounds of formula I and their acid addition salts are suitable for treatment of diseases that result from disorders of the glutamate-imparted neurotransmission. The treatment with ß-carbolines prevents or slows down cell damages and functional disorders occurring because of the disease and reduces the symptoms resulting in this way.

According to the invention ß-carbolines of formula I are suitable for the production of a pharmaceutical agent for the treatment of neurological diseases, that are based on neurodegenerative disorders such as Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, senile dementia, multiinfarct dementia or cell damages by hypoglycemia, hypoxia and ischemia or for the treatment of neuronal damages that result from uncontrolled movements or brain damage such as after stroke, brain trauma and asphyxia. Further the compounds of formula I are suitable for the treatment of psychiatric diseases such as schizophrenia, migraines and conditions of pain and for the treatment of withdrawal symptoms after drug abuse (opiates, hallucinogens, sedatives, alcohol and cocaine).

The indications can be shown by usual pharmacological tests.

The invention also comprises pharmaceutical agents that contain said compounds, their production as well as the use of the compounds according to the invention for the production of pharmaceutical agents that are used for the treatment and prophylaxis of the above-mentioned diseases. The pharmaceutical

agents are produced according to processes known in the art, by the active ingredient being brought into the form of a pharmaceutical preparation, with suitable vehicle, auxiliary and/or addition substances, a preparation that is suitable for enteral or parenteral administration. The administration can take place orally or sublingually, as a solid in the form of capsules or tablets or as liquid in the form of solutions, suspensions, elixirs or emulsions or rectally in the form of suppositories or the form of injection solutions optionally also usable subcutaneously. As auxiliary agents for the desired pharmaceutical agent formulation the inert organic and inorganic vehicles known to one skilled in the art are suitable such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. Optionally, moreover, the contents may include preservatives, stabilizers, wetting agents, emulsifiers or salts to change the osmotic pressure or buffers.

The pharmaceutical preparations can be available in solid form, for example, as tablets, coated tablets, suppositories, capsules, or in liquid form, for example, as solutions, suspensions or emulsions.

As vehicle systems interface-near auxiliary agents such as salts of bile acids or animal or vegetable phospholipids, but also mixtures of them as well as liposomes or their components, can be used.

For oral use, tablets, coated tablets or capsules with talc and/or hydrocarbon vehicles or binders, such as, for example,

lactose, corn or potato starch, are especially suitable. The use can also take place in liquid form, such as, for example, as juice, to which a sweetener is optionally added.

For parenteral use, especially injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxyethoxylated castor oil are suitable.

The dosage of the active ingredients can vary according to method of administration, age and weight of the patient, type and severity of the disease to be treated and similar factors. The daily dose can be given as a single dose administered all at once or subdivided into 2 or more daily doses. The compounds are introduced in a dosage unit of 0.05 to 100 mg of active substance in a physiologically compatible vehicle. Generally a dose of 0.1-500 mg/day, preferably 0.1 to 50 mg/day is used.

The compounds of formula I are known or can be produced analogously to known compounds and known processes. For example, the production of the compounds of formula I are described in the following protective rights: EP-30254, EP-54507, EP-128415, EP-130140, EP-130141, EP-137390, EP-161575, EP-222693, EP-234173, EP-232675, EP-237467, WO 92/21679 and DOS-4130933.2.

The following examples are to explain the production of the compounds of formula I:

Example 1

5-Benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid

15 g of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid ethyl ester are refluxed for 4 hours with 100 ml of 2N sodium hydroxide solution. In the heating the batch is adjusted lightly acidic (pH 4) with 2N hydrochloric acid, the precipitated crystallizate is suctioned off during cooling and the filter cake is washed neutral under water and dried. 13.8 g (99 % of theory) of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid of a melting point of 225°C (decomposition) is obtained.

Analogously there are produced:

6-benzyloxy-4,9-dimethyl-ß-carboline-3-carboxylic acid

4-isopropoxymethyl-ß-carboline-3-carboxylic acid

5-isopropoxy-4-methoxymethyl-ß-carboline-3-carboxylic acid

5-(5-bromopyrid-2-yl)-oxy-4-methoxymethyl-ß-carboline-3-carboxylic acid

6-pyrazinyloxy-4-ethyl-ß-carboline-3-carboxylic acid

6,7-dimethoxy-4-ethyl-ß-carboline-3-carboxylic acid

6,7-dimethoxy-4-ethyl-9-methyl-ß-carboline-3-carboxylic acid

4-methoxy-ethoxymethyl-ß-carboline-3-carboxylic acid

5-isopropoxy-4,9-dimethyl-ß-carboline-3-carboxylic acid

5-(4-Cl-phenoxy)-4-methoxymethyl-9-methyl-ß-carboline-3-carboxylic acid

5-benzyloxy-4-methoxymethyl-9-benzyl-ß-carboline-3-carboxylic acid

6-ethoxy-9-ethyl-ß-carboline-3-carboxylic acid

5-isopropoxy-4-methyl-9-ethyl-ß-carboline-3-carboxylic acid

Example 2

5-Benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid ethylamide

1.44 g (4 mmol) of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid is introduced in 40 ml of dimethylformamide and mixed at room temperature with a 0.25 molar solution of thionylimidazole in tetrahydrofuran. After stirring for 1 hour at room temperature, ethylamine is introduced in this solution for 30 minutes. The batch is concentrated by evaporation and the residue is divided in methylene chloride and water. The organic phase is dried, filtered, concentrated by evaporation and the residue recrystallized twice from ethanol/diisopropyl ester. 727 mg (47 % of theory) of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid ethylamide of a melting point of 204-206°C is obtained.

Basically analogously there are produced:

6-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid isopropylamide

4-ethyl-ß-carboline-3-carboxylic acid-(3-fluorophenyl)-amide

5-(3-chlorobenzyloxy)-4-methoxymethyl-ß-carboline-3-carboxylic acid cyclopropylamide

5-benzyloxy-ß-carboline-3-carboxylic acid amide

6-(piperidin-1-yl)-ß-carboline-3-carboxylic acid methylamide

ß-carboline-3-carboxylic acid-(1-hydroxymethyl)-propylamide

6-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid-(2-hydroxyethyl)-amide

5-isopropoxy-4,9-dimethyl-ß-carboline-3-carboxylic acid-N-ethylamide

5-(4-chlorophenoxy)-4-methoxymethyl-ß-carboline-3-carboxylic acid morpholide

Example 3

5-Benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid diethylamide

A suspension of 724 mg (2 mmol) of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid in 29 ml of absolute dimethylformamide is mixed with 32 ml of a 0.25 molar solution of thionylimidazole in tetrahydrofuran and stirred for 2 hours at room temperature. A clear solution then resulted. It is mixed with 100 ml of water and extracted three times with ethyl acetate. The organic phase is washed with saturated common salt solution, dried, filtered and concentrated by evaporation. The residue is recrystallized from ethanol/diethylether and 389 mg of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid imidazolide of a melting point of 172-175°C is obtained. This imidazolide is heated to 210°C for 2 hours in 20 ml of dimethylformamide. After concentration by evaporation the residue is chromatographed twice on silica gel first with methylene chloride:ethanol = 10:1 and then with toluene:glacial acetic acid:H_2O = 10:10:1. 100 mg of 5-benzyloxy-4-methoxymethyl-ß-carboline-3-carboxylic acid diethylamide of a melting point of 164-166°C is obtained.

Example 4

9-Methyl-5-(4-chlorophenoxy)-4-methoxymethyl-ß-carboline-3-carboxylic acid isopropyl ester

560 mg (1.3 mmol) of 5-(4-chlorophenoxy)-4-methoxymethyl-ß-carboline-3-carboxylic acid isopropyl ester in 20 ml of dimethylformamide is mixed with 45 mg of sodium hydride (dispersion, 80%) and stirred for 15 minutes at room temperature. Then 190 mg (1.3 mmol) of methyl iodide is added and stirred for 2 hours at 80°C bath temperature. After being put into water it is extracted with methylene chloride, the organic phase washed, dried, filtered and concentrated by evaporation. The residue is chromatographed on silica gel with methylene chloride:i-propanol = 90:10. 320 mg (48% of theory) of 9-methyl-5-(4-chlorophenoxy)-4-methoxymethyl-ß-carboline-3-carboxylic acid isopropyl ester of a melting point of 117-118°C is obtained.

Analogously there are produced:

5-isopropoxy-4,9-dimethyl-ß-carboline-3-carboxylic acid ethyl ester

6-benzyloxy-4,9-dimethyl-ß-carboline-3-carboxylic acid isopropyl ester

6,7-dimethoxy-4-ethyl-9-methyl-ß-carboline-3-carboxylic acid methyl ester

5-(4-chlorophenyl)-4-methoxymethyl-9-ethyl-ß-carboline-3-carboxylic acid isopropyl ester

6,7-dimethoxy-4-ethyl-9-benzyl-ß-carboline-3-carboxylic acid methyl ester

5-(4-chlorophenoxy)-4-methoxymethyl-9-isopropyl-ß-carboline-3-carboxylic acid isopropyl ester

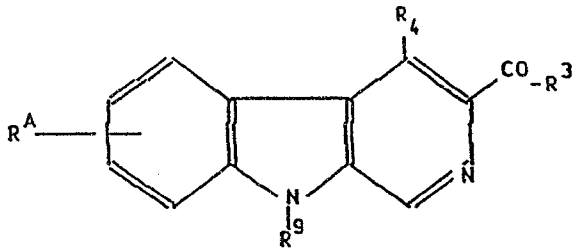
5-benzyloxy-4-methoxymethyl-9-benzyl-ß-carboline-3-carboxylic acid ethyl ester

6-ethoxy-9-ethyl-ß-carboline-3-carboxylic acid ethyl ester.

Claims

1.)

Use of compounds of formula I or their acid addition salts



I

in which

R^A means hydrogen, halogen, NH_2, NO_2, $-CHR^1-R^2$, phenyl, hetaryl, $-OR^5$ or $-CO-R$ optionally substituted with halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy or amino and can be single to triple, the same or different,

R^3 means hydroxy, C_{1-6}-alkoxy or NR^6R^7,

R^4 means hydrogen, phenyl, C_{3-7}-cycloalkyl, C_{1-6}-alkyl or $-(CH_2)_n-O-R^8$ and

R^9 means hydrogen, C_{1-6}-alkyl or benzyl, and

R is hydroxy, C_{1-6}-alkoxy, benzyloxy or $NR^{10}R^{11}$, in which R^{10} and R^{11} are the same or different and mean hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl or together with the nitrogen atom a saturated 5 or 6 membered heterocycle that also contains another sulfur, oxygen or nitrogen atom and can be substituted with phenyl or C_{1-4}-alkyl,

R^1 means hydrogen or C_{1-4}-alkyl,

R^2 means hydrogen, C_{1-2}-alkyl, $-O-C_{1-6}$-alkyl, $-S-C_{1-6}$-alkyl optionally substituted with $NR^{12}R^{13}$ or an optionally substituted phenyl, benzyl or phenoxy radical,

R^5 means hydrogen, C_{1-6}-alkyl, C_{3-7}-cycloalkyl or an optionally substituted phenyl, benzyl, hetaryl or benzo condensed hetaryl radical,

R^6 means hydrogen, C_{1-6}-alkyl or C_{2-6}-alkenyl,

R^7 means hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, $NR^{14}R^{15}$, hydroxy, C_{1-6}-alkoxy, $-CO-R^{16}$, C_{3-7}-cycloalkyl, a phenyl or phenyl-C_{1-2}-alkyl radical optionally substituted with halogen or C_{1-6}-alkyl optionally substituted with C_{1-4}-alkoxy, $NR^{17}R^{18}$, hydroxy, halogen, phenyl, C_{1-4}-alkoxycarbonyl or hydroxycarbonyl or

R^6 and R^7 together with the nitrogen atom form a 3 to 6 membered saturated heterocycle, that can contain another O or N atom and can be substituted with one to two C_{1-4}-alkyl or C_{1-4}-alkoxycarbonyl,

R^6 and R^7 together with the nitrogen atom form a 5 or 6 membered unsaturated heterocycle, that can contain another O or S atom or two other N atoms,

R^8 means hydrogen, C_{1-6}-alkyl, C_{1-4}-alkoxy-C_{1-4}-alkyl or phenyl,

R^{12} and R^{13} each mean hydrogen, phenyl, C_{1-4}-alkyl or together with the nitrogen atom form a 5 or 6 membered saturated heterocycle that can contain another O, S or N atom and can be substituted with one to two C_{1-4}-alkyl or C_{1-4}-alkoxycarbonyl,

R^{14} and R^{15} have the meaning of R^{12} and R^{13},

R^{17} and R^{18} have the meaning of R^{12} and R^{13},

R^{16} means hydrogen, C_{1-4}-alkyl or NH_2 and

n means 1, 2 or 3.

for the production of a pharmaceutical agent for the treatment of functional disorders of the quisqualate receptor.

2.)

Use of compounds of formula I or their acid addition salts according to claim 1, characterized in that neurological diseases are treated.

3.)

Use of compounds of formula I or their acid addition salts according to claim 2, wherein neurodegenerative diseases such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, stroke, brain trauma, asphyxia, multiinfarct dementia are treated.

4.)

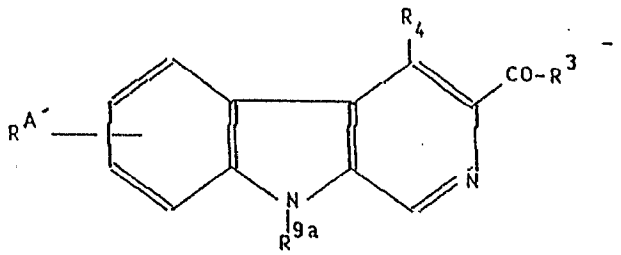
Use of compounds of formula I or their acid addition salts according to claim 2, wherein diseases such as migraine, conditions of pain or withdrawal symptoms after drug abuse are treated.

5.)

Use according to claim 2, wherein neuronal cell damages are treated.

6.)

Compounds of formula Ia



Ia

in which

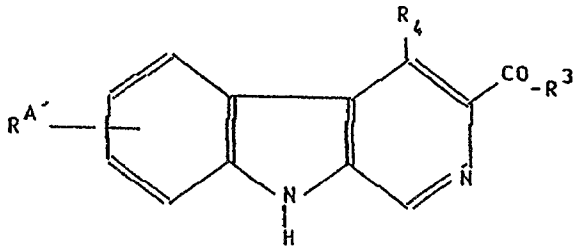
R^{9a} means C_{1-6}-alkyl or benzyl,

$R^{A'}$ means phenyl, hetaryl, $-CHR^1-R^2$, $-OR^5$ or $-CO-R$ optionally substituted with halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, or amino and can be single to triple, the same or different and

R^1, R^2, R^3, R^4, R^5 and R have the above indicated meaning.

7.)

Process for the production of the compounds of formula Ia wherein a compound of formula II



II

in which $R^{A'}$, R^4 and R^3 have the above-mentioned meaning, is optionally alkylated after protection of hydroxy groups with $R^{9a}X$, in which X means halogen and optionally present protective groups are then cleaved off or esters are saponified.

8.)

Process for the production of a pharmaceutical agent wherein the active ingredients according to claim 6 are brought into a suitable form of administration with suitable vehicle and auxiliary substances and/or additives.

9.)

Pharmaceutical agents containing a compound of formula Ia and a suitable vehicle and auxiliary substance and/or an additive.

SUBSTITUTE

REMPLACEMENT

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